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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/330,903	06/11/1999	IGOR GONDA	6513/061US1	9095

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CAROL L FRANCIS
BOZICEVIC FIELD & FRANCIS LLP
200 MIDDLEFIELD ROAD
SUITE 200
MENLO PARK, CA 94025

EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/330,903	GONDA ET AL.	
	Examiner	Art Unit	
	Richard Schnizer	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 57-71 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 57-71 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment was received and entered as Paper No. 18 on 1/16/02. Claims 21-56 were canceled and claims 57-71 were added as requested. Claims 57-71 are pending and under consideration in this Office Action.

Priority

Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 112 as follows:

> The second application (which is called a continuing application) must be an application for a patent for an invention which is also disclosed in the first application (the parent or provisional application); the disclosure of the invention in the parent application and in the continuing application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *In re Ahlbrecht*, 168 USPQ 293 (CCPA 1971).

This Application claims priority to application number 08/752,946, filed 11/21/96, now US Patent 5,906,202, issued 5/25/99. However, instant claims 57-71 recite "a polynucleotide and a condensing agent" and there is no support for this limitation in US Patent 5,906,202. Furthermore, '202 provides no support for the following claim limitations, a lipid-based carrier (instant claims 61 and 62). For these reasons, the priority date for the instant claims is considered to be that of provisional application 60/089,146 which is 6/12/98.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65 and 66 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 65 recites an aerosol composition comprising particles having a polynucleotide to protamine sulfate weight ratio of from about 2:1 to about 11:1. The specification fails to provide literal support for this range, thus it represents new matter.

Claim 66 requires the use of dextran sulfate as a condensing agent. The specification fails to provide literal support for this embodiment, thus it represents new matter.

It is further noted that the citations provided at page 4 of Applicant's response filed 6/25/01 do not provide support for the limitations discussed above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 57-71 are indefinite because they are incomplete. The methods recite no step in which the aerosol is delivered. These claims are also indefinite because they require a result without any process that could lead to the results. More particularly, step (c) of claim 57 recites the phrase "wherein aerosol particles are comprised of a polynucleotide and a condensing agent which results in condensing polynucleotide particles". The claims are indefinite because a composition cannot have a result. Only processes can have results, and the claim recites no steps which can lead to condensing polynucleotide particles. It is also unclear what is intended by "free air volume". The specification does not define this term. Further, these claims require that "aerosol volume inhaled is controlled along with free air volume inhaled prior to and following inhalation of aerosol". This could be construed as requiring the inhaled aerosol volume to be controlled before and after it is inhaled. Alternatively it could be construed as requiring the inhalation of controlled amounts of free air both before and after aerosol inhalation. It is suggested that this portion of the claim should be clarified through the recitation of steps. For example, if Applicant wished to claim a method in which aerosol-free air is inhaled both before and after inhalation of aerosol, the claim could recite *e.g.* a step requiring controlled inhalation of aerosol-free air, followed by a step requiring controlled inhalation of aerosol, followed by a step requiring controlled inhalation of aerosol-free air, or words to that effect.

Claims 58-60 are indefinite because they recite "the particle size" without proper antecedent basis. These claims depend from claim 57 which recites two distinct particles of different sizes: aerosol particles, and condensed nucleic acid particles within the aerosol particles. It is suggested that claims 58-60 should recite "the aerosol particle size", rather than "the particle size".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 57-62, 70, and 71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs (US Patent 5,756,353, issued 5/26/98), Crook et al (Gene Therapy 3(9): 834-839, 9/1996). Schuster et al (US Patent 5,906,202, issued 5/25/99), and Radhakrishnan (US Patent 5,049,389, issued 9/17/91).

Debs teaches a method of targeting an area of a patient's respiratory tract by delivering to the patient an aerosol comprising DNA condensed with small unilamellar cationic liposomes. See abstract and column 11, lines 24-26. The lipid may be DOTAP or DOTMA. See claim 3, column 15. The size of the aerosol particles is adjusted based on the intended delivery site within the respiratory tract. A size range of from 0.5-5 microns is suggested for alveoli, and a

size range of 5-10 microns is suggested for airway delivery. See column 12, lines 51-56, 60, and 61; and claims 1, and 14-16.

Debs does not teach inhaling controlled amounts of aerosol-free air prior to and after inhaling a controlled amount of aerosol, or adjusting inspiratory flow rate. Debs teaches the use of small unilamellar vesicles, but is silent as to their size, as such Debs does not teach polynucleotide particles in the size range of 20-50 nanometers.

Crook teaches that DOTAP-encapsulated plasmid DNA is considered to be condensed. See abstract.

Schuster teaches a device and method of delivering a volume of aerosol to a target area of a lung. The method comprises measuring a volume of particle-free air inhaled into the lungs, drawing a measured volume of aerosol into the respiratory tract, and inhaling additional particle-free air, insufficient to fill the upper region of the patient's respiratory tract. See claim 6, bridging columns 38 and 39. Schuster teaches the delivery of gene vectors by this method. See column 2, line 33; paragraph bridging columns 30 and 31, and claims 11-13. The method involves adjusting the size of aerosol particles during delivery. See column 12, lines 37, 38, and 47-49; and paragraph bridging columns 20 and 21. Schuster teaches using aerosol particle sizes from 1-10 microns in aerodynamic diameter, and the adjustment of particle size in order to target specific regions of the respiratory system.. See column 20, lines 30-50. Schuster also teaches adjusting inspiratory flow rate to 0.2 to 3 liters per second. See column 12, lines 34-36.

Radhakrishnan teaches that depth of penetration of aerosol particles into the respiratory tract is inversely related to the aerodynamic diameter of the particles. See e.g. Fig. 3. Radhakrishnan also teaches the use of small unilamellar vesicles ranging in size from 20-70 nanometers, noting that such vesicles are advantageous because they provide greater packing density at the mucosal surface than do larger vesicles. See column 10, lines 1-10.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the delivery device and method of Schuster in the method of Debs. One would have been motivated to do so because Debs teaches that the choice of a nebulizer system will vary with the choice of target site (see column 12, lines 37-47) and Schuster teaches a single device and method which allow efficient targeting of the aerosol particles to desired areas of the lung. See column 2, lines 4-9. It would have been obvious to use small unilamellar particles in the size range of 20-50 nm because Radhakrishnan teaches that such vesicles provide greater packing density at the mucosal surface than do larger vesicles.

It would have been obvious to adjust the size of aerosol particles to particular aerodynamic diameters in order to target various sites in the respiratory tract, because both Debs and Schuster suggest that this should be done. The size of the particles is clearly a result effective variable, the optimization of which is routine in the art particularly in view of Radhakrishnan who establishes the relationship between particle size and depth of penetration into the respiratory tract.

Thus the invention as a whole was *prima facie* obvious.

Claims 63-65, and 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs, Crook, Schuster, and Radhakrishnan as applied to claims 57-62, 70, and 71 above, and further in view of Gao et al (US Patent 5,795,587, issued 8/18/98) and Curiel et al (US Patent 5,547,932, issued 8/20/96).

The teachings of Debs, Crook, Schuster, and Radhakrishnan are summarized above, and can be combined to render obvious a method of targeting an area of a patient's respiratory tract by delivering an aerosol containing a condensed polynucleotide while adjusting both the particle size in the aerosol and the volume inhaled.

These references do not teach a polynucleotide condensed with protamine sulfate, polylysine, spermine, spermidine or polyethyleneimine..

Gao teaches stable lipid-comprising nucleic acid delivery particles in which the nucleic acid is complexed with either polylysine or protamine. See column 9, line 40 to column 10 line 11, especially column 10, lines 6-11. See also claims 4 and 11. The particles may be delivered as an aerosol. See column 11, lines 30-34.

Curiel teaches the use of polylysine, polyethyleneimine, protamine, spermine, and spermidine as DNA condensing agents, as well as the subsequent delivery of the condensed DNA to lung tissue by aerosol administration. See column 25, lines 21-32, and column 36, lines 6-17.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use such polycations as protamine sulfate, polylysine, polyethyleneimine, spermine, or

spermidine or polylysine to condense the DNA of Debs prior to formation of an aerosol, as taught by Gao. One would have been motivated to do so because Gao teaches that lipid/nucleic acid/polycation complexes are highly concentrated, stable, and retain biological activity for prolonged periods of time.

In further consideration of claim 62, it is also noted that Gao teaches the use of DC-Chol in the formation of the complexes. See column 8, lines 7 and 8.

Thus the invention as a whole was prima facie obvious.

Response to Arguments

Applicant's arguments filed 1/16/02 have been fully considered as they apply to the rejections set forth above, but they are not persuasive.

At page 6 of the response, Applicant states that specific support for the claimed methods has been pointed out and that the rejection under 35 USC 112, first paragraph is rendered moot. This is unpersuasive because, as noted in Paper No. 17, the specification fails to support an aerosol composition comprising particles having a polynucleotide to protamine sulfate weight ratio of from about 2:1 to about 11:1. Applicant has not pointed to any support for this range of ratios.

At page 6 of the response, Applicant states that the combination of Debs and Schuster is not realistic because Debs does not teach towards the adjustment of particle size in order to target

areas of the lungs. This is unpersuasive because the claims do not require targeting of specific areas of the lungs, the claims require targeting to specific areas of the respiratory tract. Applicant's attention is directed to column 12, lines 51-61 of Debs which teaches that specific areas of the respiratory tract can be targeted by adjusting aerosol particle size of condensed nucleic acid particles. For these reasons the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER